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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,819	01/17/2001	Christopher J. Stanley	PM 275510 P5642US	5588

25225 7590 12/23/2005

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,819	STANLEY, CHRISTOPHER J.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2005* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-26 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-26 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2001 (original)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/313,385* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on September 23, 2005 has been entered. The claims pending in this application are claims 1, 3-26, and 28-34. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on September 23, 2005.

Claim Objections

2. Claim 1 is objected to because of the following informality: there should be a word "and" before the phrase "performing amplification of the nucleic acid template" in last line of the claim.

3. Claims 4-17 are objected to because of the following informality: "A process" should be "The process".

4. Claim 20 is objected to because of the following informality: "was" in last line of the claim should be "is".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 19 is rejected as vague and indefinite. According to claim 17, said carrier macromolecule bound to replicated template has a molecule weight in excess of 80,000 Dalton while according to claim 18, said carrier macromolecule bound to nucleic acids has a molecule weight in excess of 100,000 Dalton. Therefore, the first part and the second part of the claim do not correspond each other. Please clarify.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Campbell (US H1398, published on January 3, 1995)

Regarding claim 1, Campbell teaches providing a primer covalently bound to a non-nucleotide carrier macromolecule (ie., fluorescein), hybridizing the bound primer to said template (ie., the target DNA from the crude preparation); and extending said primer to form an extended primer (ie., amplified product) and performing amplification of the nucleic acid template as recited in the claim. Since fluorescein has an OH- group and is water soluble (see attachment for fluorescein in the office action mailed on May 25, 2005) and the specification

does not define "macromolecule" and it is known that OH- group is a nucleophilic functional group, Campbell discloses that said carrier macromolecule (ie., fluorescein) is water soluble at a temperature in the range of 0-60°C wherein said carrier macromolecule is a synthetic polymer (ie., a polymer comprising CH monomers) having nucleophilic functional groups as recited in the claim (see columns 2 and 3).

Therefore, Campbell teaches all limitations recited in claim 1.

10. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Bronstein (US Patent No. 5,220,005, published on June 15, 1993).

Regarding claim 18, Bronstein teaches to hybridize a DNA probe labeled with alkaline phosphatase with nucleic acids immobilized on a nitrocellulose membrane and detect the hybridization (see column 13, lines 44-61). Since alkaline phosphatase is directly and covalently attached to the DNA probe and it is known that alkaline phosphatase has a molecular weight in excess of 100,000 Daltons, the DNA probe taught by Bronstein is a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 100,000 Daltons (ie., alkaline phosphatase) as recited in the claim. Since it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose in previous office action mailed on January 7, 2004), a nucleic acid that is complementary with the DNA probe and is immobilized on a nitrocellulose membrane is a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 100,000 Daltons (3,000 ×180.2=540,600 Daltons) as recited in the claim. Since Bronstein teaches to

hybridize a DNA probe labeled with alkaline phosphatase with nucleic acids immobilized on a nitrocellulose membrane and detect the hybridization (see column 13, lines 44-61), Bronstein discloses contacting said first and second nucleic acids under hybridization conditions and detecting hybridization between said first and second nucleic acids as recited in the claim.

Therefore, Bronstein teaches all limitations recited in claim 18.

Response to Arguments

In page 9, sixth paragraph bridging to page 11, first paragraph of applicant's remarks, applicant argues that: (1) "[A] person of ordinary skill would not regard a nitrocellulose membrane as a 'carrier macromolecule', or even as being a macromolecule at all, as the Examiner contends. Indeed, the use of the term in the specification excludes this strained interpretation. The specification states 'In a particularly advantageous aspect of the invention, the carrier macromolecule is itself bound to a solid support' (paragraph 24). And again at paragraph 32, 'The invention includes also a nucleic acid bound to a carrier macromolecule, which macromolecule is itself bound to a solid support and the use of such an immobilized nucleic acid as a primer or probe'. Therefore, the specification makes it clear that a membrane or solid phase is not a 'carrier macromolecule'."; and (2) "[B]ronstein discloses the presence of alkaline phosphatase on one of the nucleic acids in the hybridization, while claim 18 requires that a first nucleic acid is bound to a non-nucleotide carrier macromolecule, and a second nucleic acid is also bound to a non-nucleotide carrier macromolecule. In view of the above explanation, Bronstein does not disclose that a nucleic acid bound to a non-nucleotide carrier macromolecule can be detected by detecting the hybridization between the first and second nucleic acids, which

is also required by the claim. Claim 18 requires that both nucleic acids are bound to a non-nucleotide carrier, which is not disclosed or suggested by Bronstein".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since there is no definition for "carrier macromolecule" in the specification and it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose in previous office action mailed on January 7, 2004), it is reasonably considered nitrocellulose membrane as a non-nucleotide carrier macromolecule. Second, the claim does not require that carrier macromolecule is itself bound to a solid support. Third, since alkaline phosphatase is directly and covalently attached to the DNA probe and it is known that alkaline phosphatase has a molecular weight in excess of 10,000 Daltons, the DNA probe taught by Bronstein is a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 10,000 Daltons (ie., alkaline phosphatase). Since it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose in previous office action mailed on January 7, 2004), a nucleic acid taught by Bronstein that is complementary with the DNA probe and is immobilized on a nitrocellulose membrane is a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 100,000 Daltons (3,000 ×180.2=540,600 Daltons).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell (US H1398, published on January 3, 1995) in view of Ausubel *et al.,* (US Patent No. 6,004,783, priority date: May 17, 1996).

Regarding claim 1, Campbell teaches providing a primer covalently bound to a non-nucleotide carrier macromolecule (ie., fluorescein), hybridizing the bound primer to said template (ie., the target DNA from the crude preparation); and extending said primer to form an extended primer (ie., amplified product) and performing amplification of the nucleic acid template as recited in the claim. Since fluorescein has an OH- group and is water soluble (see attachment for fluorescein in the office action mailed on May 25, 2005) and the specification does not define "macromolecule" and it is known that OH- group is a nucleophilic functional group, Campbell discloses that said carrier macromolecule (ie., fluorescein) is water soluble at a temperature in the range of 0-60°C as recited in the claim (see columns 2 and 3).

Campbell does not disclose that said carrier macromolecule is a polypeptide as recited in claim 1.

Ausubel *et al.,* teach that fluorescent labels and enzymes such as alkaline phosphatase are used to label a primer (see column 27, fourth paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 wherein said carrier macromolecule is a polypeptide (ie., alkaline phosphatase) in view of the prior art of Campbell and Ausubel *et al.*. One having ordinary skill in the art would have been motivated to do so because Ausubel *et al.,* teach that fluorescent labels and enzymes such as alkaline phosphatase are used to label a primer (see column 27, fourth paragraph) and the simple replacement of one well known label (ie., the fluorescent label taught by Campbell) from another well known label (i.e., alkaline phosphatase taught by Ausubel *et al.,*) during the process for making a primer recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the fluorescent label taught by Campbell and alkaline phosphatase taught by Ausubel *et al.,* are used for the same purpose (ie., labeling a primer) and are exchangeable.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

13. Claims 3-9, 11-13, 24-26, 28, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Ausubel *et al.,* as applied to claim 1 above, and further in view of Gold *et al.,* (US Patent NO. 6,011,020, filed on May 4, 1995).

Regarding claim 3, since claim 1 contains all limitations recited in claim 3 except claim 3 requires a primer bound to a non-nucleotide carrier macromolecule via one or more moieties derived from divinyl sulfone, Campbell in view of Ausubel *et al.,* disclose providing a primer bound to a non-nucleotide carrier macromolecule (ie., alkaline phosphatase), hybridizing the bound primer to said template (ie., the target DNA from the crude preparation); and extending said primer to form an extended primer (ie., amplified product) which replicates from said template wherein the non-nucleotide carrier macromolecule is a polypeptide (ie., alkaline phosphatase) as recited in the claim.

Regarding claims 8, 9, 11, 13, 28, and 30, since Campbell teaches that said primer is extended by a polymerase wherein said polymerase incorporates nucleotides into said primer wherein said primer is extended in a polymerase chain amplification and said template is a double stranded template and is denatured to a single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 8, 9, 11, 28, and 30 (see columns 2 and 3). Since the specification does not define "carrier macromolecule" and Campbell teaches a primer having a site for double stranded DNA binding protein in its 5' end (column 3), Campbell discloses a

second primer with a carrier macromolecule (ie., a site for double stranded DNA binding protein) as recited in claims 13.

Regarding claim 12, since Campbell teaches to attach amplified product on a support (see column 4, second paragraph), Campbell discloses said carrier macromolecule (ie., fluorescein) is bound to a solid support after the amplification as recited in claim 12.

Regarding claims 4-6, Ausubel *et al.,* teach that said carrier macromolecule (ie., alkaline phosphatase) has a molecular weight in excess of 80,000 Daltons as recited in claims 5 and 6.

Campbell and Ausubel *et al.,* do not disclose a primer covalently bound to a carrier macromolecule via one or more moieties derived from divinyl sulfone as recited in claims 3 and 7 wherein the carrier macromolecule is dextran or dextran derivative as recited in claim 24 and said dextran is bound to solid support as recited in claim 31.

Gold *et al.,* teach a nucleic acid covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone (see column 8, fourth paragraph and column 18, second paragraph).

Regarding claims 4 and 24-26, since it is known that dextran is a linear polysaccharide made of many glucose molecules joined into a long chain and dextran/salt solutions are sometimes used to replace lost blood in emergency situation (see attachment for dextran in the office action mailed on May 25, 2005), dextran must be water soluble with pH of 4-10. Thus Gold *et al.,* disclose that the carrier macromolecule (ie., dextran) in its free state is substantially linear and substantially charged at a pH in the range of 4 to 10 as recited in claims 4, 24, and 25. Since dextran taught by Gold *et al.,* is 1000 Da or more (see column 8, lines 45-53), Gold *et al.,*

disclose that said dextran has a peak molecular weight in the range of 1,000 to 40,000,000 as recited in claim 26.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 using a primer covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone in view of the prior art of Campbell, Ausubel *et al.,* and Gold *et al.*. One having ordinary skill in the art would have been motivated to do so because Gold *et al.,* have successfully made a nucleic acid covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone and the simple replacement of one well known label (ie., alkaline phosphatase taught by Ausubel *et al.,*) from another well known label (i.e., dextran taught by Gold *et al.,*) during the process for making a primer recited in claim 3 or 7 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because both alkaline phosphatase and dextran are used for the same purpose (ie., using as oligonucleotide labels).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

14. Claims 10, 14-17, 29, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell, Ausubel *et al.*, and Gold *et al.*, as applied to claims 3-9, 11-13, 24-26, 28, 30, and 31 above, and further in view of Landegren *et al.*, (US Patent No. 4,988,617, published on January 29, 1991).

The teachings of Campbell, Ausubel *et al.*, and Gold *et al.*, have been summarized previously, *supra*.

Campbell, Ausubel *et al.*, and Gold *et al.*, do not disclose that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claims 10 and 29, said another primer which is ligated by said ligase is also bound to a carrier macromolecule wherein during the extension, a detectable marker is incorporated into one of the extended primers as recited in claims 14 and 15, said extension of one of the primers is conducted *in situ* in a biological sample wherein said biological sample is a plant or animal tissue sample, microorganism culture, or microorganism culture medium as recited in claims 16, 17, 32, and 33.

Landegren *et al.*, teach a ligase chain reaction using two primers with different labels (see Figure 1, column 4, lines 12-50, column 8, lines 43-46, and column 10, last paragraph). Since the specification does not define "carrier macromolecule" and biotin on one of the primers taught by Landegren *et al.*, is a carrier molecule and a detectable marker as recited in claims 14 and 15. Therefore, Landegren *et al.*, teach that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claims 10 and 29, said another primer which is ligated by said ligase is also bound to a carrier macromolecule wherein during the extension, a detectable marker is incorporated into one of the

extended primers as recited in claims 14 and 15. Since Landegren *et al.,* teach to use DNA from sickle cell patient for *in situ* analysis, Landegren *et al.,* disclose that said extension of one of the primers is conducted *in situ* in a biological sample wherein said biological sample is an animal tissue sample as recited in claims 16, 17, 32, and 33.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 10, 14, and 15 in view of the prior art of Campbell, Ausubel *et al.,* Gold *et al.,* and Landegren *et al.*. One having ordinary skill in the art would have been motivated to do so because Landegren *et al.,* have successfully extended a primer by ligase chain reaction using two primers with different labels and the simple replacement of one well known replication method (i.e., the method taught by Walker *et al.,*) from another well known replication method (i.e., the method taught by Landegren *et al.,*) during the process of performing the methods recited in claims 10 and 14-17 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Walker and the method taught by Landegren *et al.,* are functional equivalent methods which are used for the same purpose (ie., extending a primer).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

15. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Ausubel *et al.,* and Gold *et al.,* as applied to claims 3-9, 11-13, 24-26, 28, 30, and 31 above, and further in view of Yamane *et al.,* (US Patent No. 4,876,335, published on October 24, 1989).

The teachings of Campbell, Ausubel *et al.,* and Gold *et al.,* have been summarized previously, *supra.*

Campbell, Ausubel *et al.,* and Gold *et al.,* do not disclose that said carrier macromolecule is a homopolyamino acid.

Yamane *et al.,* teach to use a polylysine-labeled oligonucleotide for hybridization (see abstract). Lysine residues on the polylysine can be any desired numbers wherein the polylysine is covalently connected to the oligonucleotide (see column 2).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 34 wherein the said carrier macromolecule is a homopolyamino acid (ie., polylysine) in view of the prior art of Campbell, Ausubel *et al.,* Gold *et al.,* and Yamane *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of label (ie., the polypeptide such as alkaline phosphatase taught by Ausubel *et al.,*) from another kind of label (i.e., the polypeptide such as polylysine taught by Yamane *et al.,*) during the process for making a primer recited in claim 34 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would enhance the hybridization between the nucleic acid template and the primer since the polylysine-labeled oligonucleotide taught by Yamane *et al.,* carries positive charges.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

16. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell, Ausubel *et al.,* Gold *et al.,* and Landegren *et al.,* as applied to claim 1 and 3-17, above, and further in view of Barany *et al.,* (US Patent NO. 6,027,889, priority date: May 28, 1996).

The teachings of Campbell, Ausubel *et al.,* Gold *et al.,* and Landegren *et al.,* have been summarized previously, *supra.*

Campbell, Ausubel *et al.,* Gold *et al.,* and Landegren *et al.,* do not disclose using the probe to detect the nucleic acid sequence in a sample by hybridization thereto as recited in claim 20. However, as shown above, Campbell, Ausubel *et al.,* Gold *et al.,* and Landegren *et al.,* teach making a probe for detecting said sequence by using said sequence as a template sequence in the method as claimed in claim 17 such that a probe comprises said extended primer that has a sequence complementary to said sequence to be detected is bound to said carrier macromolecule, removing any free nucleic acid not bound to said carrier macromolecule thereof as recited in claim 20.

Barany *et al.,* teach using the ligated probe to detect the nucleic acid sequence in a sample by hybridization (see Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 20 in view of the prior art of Campbell, Ausubel *et al.,* Gold *et al.,* Landegren *et al.,* and Barany *et al.*. One having ordinary skill in the art would have been motivated to do so because Barany *et al.,* have successfully used a ligated product as a probe for a hybridization assay (see Figure 1). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to use a ligated product recited in claim 17 as a probe for a hybridization assay.

17. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.,* (US Patent NO. 6,011,020, filed on May 4, 1995).

Regarding claim 21, Gold *et al.,* disclose an immobilized nucleic acid comprising a nucleic acid linked via one or more moieties derived from vinyl sulfone to a non-nucleotide carrier macromolecule (ie., PEG), which the non-nucleotide carrier macromolecule is directly bound to a solid support such as membrane as recited in claim 21 (see column 6, third paragraph, column 8, fourth paragraph and column 18, second paragraph).

Gold *et al.,* do not disclose that a non-nucleotide carrier macromolecule is dextran. However, Gold *et al.,* teach that different non-immunogenic, high molecular weight compounds such as PEG and dextran are used to modify a nucleic acid ligand (see column 8, lines 45-53 and column 18, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made an immobilized nucleic acid comprising a nucleic acid linked via one or more moieties derived from divinyl sulfone to a non-nucleotide carrier macromolecule such as dextran which the non-nucleotide carrier macromolecule is directly bound to a solid support such as a membrane recited in claim 21 in view of the patent of Gold *et al.*. One having ordinary skill in the art would have been motivated to do so because Gold *et al.*, have successfully made a nucleic acid covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone and the simple replacement of one kind of non-immunogenic, high molecular weight compound (ie., PEG) from another kind of non-immunogenic, high molecular weight compound (ie., dextran) during the process for making an immobilized nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because both PEG and dextran are non-immunogenic, high molecular weight compounds and are used to modify a nucleic acid and they are exchangeable (see column 8, lines 45-53).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

18. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.*, (1995) as applied to claim 21 above, and further in view of Urdea (US Patent No. 4,775,619, published on October 4, 1988).

The teachings of Gold *et al.*, have been summarized previously, *supra*.

Gold *et al.*, do not disclose formulating the immobilized nucleic acid recited in claim 21 as a hybridization probe and introducing the immobilized nucleic acid into a hybridization utilizing the hybridization probe as recited in claim 22.

Urdea teaches to perform a hybridization of a nucleic acid immobilized on a membrane to a sample containing a DNA fragment (see column 11, lines 5-19).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have formulated the immobilized nucleic acid recited in claim 21 as a hybridization probe and introduced the immobilized nucleic acid into a hybridization utilizing the hybridization probe recited in claim 22 in view of the patents of Gold *et al.*, and Urdea. One having ordinary skill in the art would have been motivated to do so because Urdea indicates that a nucleic acid immobilized on a membrane is used for hybridization with a sample containing a DNA fragment (see column 11, lines 5-19). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to formulate the immobilized nucleic acid recited in claim 21 as a hybridization probe and introduce the immobilized nucleic acid into a hybridization utilizing the hybridization probe.

Response to Arguments

In page 14, second paragraph of applicant's remarks, applicant argues that "[G]old et al. fail to teach nucleic acids comprising a non-nucleotide carrier macromolecule that is directly bound to such solid supports".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Gold *et al.,* do teach nucleic acids comprising a non-nucleotide carrier macromolecule that is directly bound to such solid supports (see column 6, third paragraph, column 8, fourth paragraph and column 18, second paragraph).

19. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.,* (US Patent No. 5,470,723, filed on August 23, 1993) in view of Westling *et al.,* (US Patent No. 5,700,921, filed on November 27, 1995).

Regarding claim 23, Walker *et al.,* teach polymerase extension of a labeled primer specifically hybridized to a target or control sequence wherein the label is alkaline phosphatase (see column 9, first and second paragraphs), Walker *et al.,* disclose providing a primer bound to a non-nucleotide carrier macromolecule (ie., alkaline phosphatase), hybridizing the bound primer to said template (ie., the target or control sequence); and extending said primer to form an extended primer (ie., the extension product of the labeled primer) which replicates from said template wherein the carrier is a polypeptide (ie., alkaline phosphatase) as recited in the claim.

Walker *et al.,* do not disclose a primer bound to a carrier macromolecule via one or more moieties derived from divinyl sulfone wherein alkaline phosphatase is a polypeptide as recited in claim 23.

Westling *et al.,* teach that an oligonculeotide is bound to said carrier macromolecule (ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone (see columns 10 and 11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claim 23 wherein said primer is bound to said carrier macromolecule (ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone in view of the patents of Walker *et al.,* and Westling *et al.*. One having ordinary skill in the art would have been motivated to do so because Westling *et al.,* have successfully bound an oligonculeotide to a carrier macromolecule (ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone, and the simple replacement of one well known method (i.e., the method taught by Walker *et al.,*) from another well known method (i.e., the method taught by Westling *et al.,*) during the process of bonding a primer to a carrier macromolecule (ie., alkaline phosphatase) would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because bonding a primer to a carrier macromolecule taught by Walker *et al.,* and bonding a primer to a carrier macromolecule taught by Westling *et al.*, are functional equivalent methods which are used for the same purpose (ie., bonding a primer to a carrier macromolecule (ie., alkaline phosphatase).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 11, last paragraph, page 13, last paragraph bridging to page 14, first paragraph, and page 14, last paragraph of applicant's remarks, applicant argues that (1) "[W]alker does not describe a method using a primer covalently bound to a carrier molecule for the amplification of a nucleic acid template"; (2) "[N]one of these references provide a motivation for making the proposed combinations. None of the references discloses a method involving the use of a primer bound to a non-nucleotide carrier macromolecule from the groups recited in the claim, hybridization of the primer to a nucleic acid template, and the extension of the primer and replication of the nucleic acid template, as recited in the claims"; and (3) the rejections are based on impermissible hindsight.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the claim 23 does not require that a primer is covalently bound to a carrier molecule as argued by applicant. Second, although none of these references provide a motivation for making the proposed combinations, there are motivations for making the proposed combinations (see above rejections) and the rejections are not based on a single reference but are based on combination of the references. Third, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. No claim is allowed.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Frank Lu
Primary Examiner
December 15, 2005